submitting herewith at Exhibit 1, a marked up copy of each amended paragraph in the specification showing all changes relative to the specification as originally filed. Applicants also submit herewith a Submission of Substitute Drawings transmittal, including Exhibits A-B with substitute **FIGS. 2, 3, 4C, 4D, 7, 8, 9,10, 12, 19 and 23** for entry in this application.

It is believed that no fees are required for this amendment. However, should the U.S. Patent and Trademark Office determine that any additional fees are required or that a refund is owed for this application, the Commissioner is hereby authorized and requested to charge the required fee(s) and/or credit the refund(s) owed to Deposit Account No. 04-0100.

Please amend the application as follows:

IN THE DRAWINGS:

Please delete **FIGS. 2, 3, 4C, 4D, 7, 8, 9, 10, 12, 19 and 23** as originally filed for this application and enter, in their place, substitute **FIGS. 2, 3, 4C, 4D, 7, 8, 9, 10, 12, 19 and 23** attached at Exhibit Tab A of the accompanying Submission of Substitute Drawings.

IN THE SPECIFICATION:

Please amend the specification as follows:

Amend page 1at line 11 of the specification by inserting the following new paragraph which reads as follows:

A1

- - Work leading to this invention was supported by Grant No. N00014-96-1-0340 awarded by the United States Navy. The United States government may have certain rights to this invention, pursuant to the term of that grant. - -

Amend the paragraph at lines 24-27 on page 15 of the specification, as indicated in the accompanying Exhibit 1, so that the paragraph reads as follows:

A2

- - **FIG. 3** is a gene alignment for β-lactamase-like genes, (1) *Enterobacter cloacae,* **SEQ. ID NO.1**; (2) *Citrobacter freundii,* **SEQ. ID NO. 2**; (3) *Yersinia enterocolitica* , **SEQ. ID NO.3**; *and* (4) *Klebsiella pneumonia,* **SEQ. ID NO.4**. SWISPROT or TrEMBL accession numbers for the protein sequences and GenBank accession numbers for the DNA sequences are given. - -

Amend the paragraph at lines 1-3 on page 17 of the specification, as indicated in the accompanying Exhibit 1, so that the paragraph reads as follows:

A3

- - **FIG. 7** is an example of an *in vitro* method of overlap extension reassembly, targeting identified crossover locations. The appropriate fragments may be obtained by split-pool synthesis. In **FIG. 7**, part (A), all possible recombinants are prepared by crossover at positions 1 and 2. In **FIG 7**, part (B), the recombinants can be prepared by assembly of synthetic fragments containing the crossover positions. This example requires fragments (plus end primers). - -

Amend the paragraph at lines 4-7 on page 17 of the specification, as indicated in the accompanying Exhibit 1, so that the paragraph reads as follows:

--**FIG. 8**, part (A), shows a fragment reassembly method using a parental template. The synthetic fragments are extended against a parent template strand and the gaps are repaired. In **FIG. 8**, part (B), the resulting products are subjected to heteroduplex recombination (Volkov *et al., Nucl. Acids Res.*, 27:18 (1999))to create libraries of genes within regions of non-identity. More complexity can be introduced by the addition of more fragments during template assembly. --

Amend the paragraph at lines 8-9 on page 17 of the specification, as indicated in the accompanying Exhibit 1, so that the paragraph reads as follows:

--**FIG. 9** shows the preparation of gene fragments prepared by PCR with primers directed to regions targeted for crossovers. In **FIG. 9**, part (A), the fragments are prepared by PCR with primers. The PCR reactions are performed with primers 1+2, 3+4 and 5+6. The method is repeated for the other parents.--

Amend the paragraph at lines 10-11 on page 17 of the specification, as indicated in the accompanying Exhibit 1, so that the paragraph reads as follows:

--**FIG. 10** shows recombination directed to specific sites using crossover primers in DNA shuffling. In **FIG. 10**, part (A), crossover primers designed to have crossovers at designated positions (2 primers for each position) are prepared. In **FIG. 10**, part (B), the parent genes are fragmented and reassembled, utilizing PCR

A3

methods, in the presence of the crossover primers to promote recombination at designated positions.- -

Amend the paragraph at lines 14-15 on page 17 of the specification, as indicated in the accompanying Exhibit 1, so that the paragraph reads as follows:

- - **FIG. 12** is a flow diagram illustrating one embodiment of a recombinant search algorithm of the invention, based upon sequence identity. In **FIG. 12**, part (1), the parent sequences are aligned with the template structure. In **FIG 12**, part (2), all possible crossover points are determined according to a sequence identity algorithm . In **FIG. 12**, part (3), the coupling matrix is calculated. In **FIG. 12**, part (4), a start parent is picked at random and copied to the offspring until a possible cut point is reached. In **FIG. 12**, part (5), a random number is picked, and if the number is less than *p*, a random new parent is copied until the next cut point is reached. In **FIG. 12**, part (6), the crossover disruption of the offspring gene is determined. - -

Amend the paragraph at lines 16-26 on page 18 of the specification, as indicated in the accompanying Exhibit 1, so that the paragraph reads as follows:

- - **FIG. 19** is a schematic demonstrating the utility of a contact map in identifying compact units of substructure. A representative contact map is on the left. The graph on the right is a statistical study of the average length of contiguous residues that can fold into a sphere of the indicated diameter (Gilbert 1998). This information can be used in the following way. If a 15-residue segment can fold into a sphere with a diameter of 21 angstroms, then this segment could be considered as

being of average compactness. However, if a 20-residue segment can fold into a sphere of 21 angstroms, this is considered as having a significantly above-average compactness. This is visualized on the contact map as a triangle on the diagonal formed by the cut points required to generate the segment. If the segment fits into a sphere of the specified diameter, then the triangle will be entirely white (interacting). The contact map shows residues that are distant (black) and residues that are close (white). If a given segment, ▬▬, folds an above average number of residues into a given sphere size, then it is compact.- -

A5

Please amend the specification at page 122, line 21, as indicated in the accompanying Exhibit 1, so that the paragraph reads as follows:

- - To test our ability to predict crossover locations, we designed experiments to recombine fragments of two beta-lactamases, TEM-1 and PSE-4, using the SOEing procedure to piece together fragments by PCR (Horton, R. M., (1995) *Mol. Biotech.* 3, 93-99). While the proteins in this example have only 40% amino acid sequence identity, they share similar structures (TEM-1 , SEQ ID NO: 5; and PSE-4 SEQ ID NO: 6) (Jelsch, C., Mourey, L., Masson, J. M., & Samama, J. P., (1993) *Proteins* 16, 364; Lim, D., Sanschagrin, F., Passmore, L., De Castro, L., Levesque, R. L., & Strynadna N. C. J., (2001) *Biochemistry* 40, 395). - -

A6

Please delete pages 126 to 155 as originally filed for this application and enter, in their place, substitute pages 126-156 attached at Exhibit 2 of the accompanying amendment.